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Factors associated with phenoconversion of idiopathic rapid eye movement sleep behavior disorder: a prospective study

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This study explores the effect of risk factors on the progression of idiopathic rapid eye movement (REM) sleep behavior disorder (iRBD) to α-synucleinopathies in a Chinese cohort. Patients with iRBD were enrolled and assessed for environmental factors and lifestyle using standardized structured questionnaires at baseline. All patients were prospectively followed for phenoconversion monitoring. The cumulative incidence was estimated using survival analysis. Of 155 iRBD enrolled in the cohort, follow-up information was available in 141 patients. The phenoconversion rate was 16.3% after 3 years, 27.6% after 5 years, and 57.2% after 10 years. Eighteen participants converted within 3 years, 27 converted within 5 years, and 36 converted within 10 years. IRBD with positive family history of parkinsonism had an increased risk of being converted to α-synucleinopathies, while tea drinking was associated with a decreased phenoconversion risk. Our findings shed light on a potential application of tea drinking in modifying iRBD progression.

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by loss of normal muscle atonia and dream enactment during REM sleep[1]. Idiopathic or isolated RBD (iRBD) is currently recognized as a critical prodromal stage with a high risk of progressing to α-synucleinopathies[2–4]. Previous studies have suggested that more than 80% of patients with iRBD could convert into Parkinson's disease (PD), dementia of Lewy bodies (DLB), and multiple system atrophy (MSA) after years or decade[2], indicating that iRBD may be an optimal target for early intervention and neuroprotective treatment. Previous case-control and retrospective cohort studies have shown that PD and its prodromal stage, e.g. iRBD, may share similar risk factors, including aging, genetic variants, some environmental exposures and lifestyle habits[5–8]. The facts that significant number of PD patients never had iRBD and iRBD patients progressed to α-synucleinopathies in a different rate or speed support the notion that there are specific factors might influence or contribute to the course of phenoconversion. Identifying those specific factors and development of intervention strategies could have significant impact not only in the understanding of the mechanisms of the diseases but also in modifying the disease course. However, these factors are yet poorly understood.

Although the cause of iRBD remains unknown, previous epidemiological studies have found that risk factors for PD or dementia, e.g. aging, gender, lower level of education[9,10], head injury[6,10], pesticide exposure[6,8], farming[6], and carbon monoxide (CO) poisoning[8], were also associated with increased risk for iRBD. In contrast, there were also lifestyle factors uniquely identified for increased risk for iRBD but not PD, e.g. smoking[8,9] and alcohol use[9]. Regarding the risk factors for phenoconversion to α-synucleinopathies in iRBD, only two longitudinal studies in the same multicenter cohort have investigated whether these factors play a role in the progression and phenoconversion at 4 years and 11 years follow-up[11,12]. According to the studies, certain factors including age, rural living, prior pesticide exposure, nitrate derivative use, lipid-lowering medication use, and respiratory medication use, were demonstrated to affect the phenoconversion of iRBD. Nonetheless, the majority of the patients in the previous studies were from Europe and North America, and variations in environments and lifestyles exist among nations and regions. Specifically, tea drinking as a protective effect was mostly found in Asians but not Caucasian[13,14]. Therefore, the current study aimed to investigate the relationship between environmental/lifestyle factors and the conversion of iRBD to α-synucleinopathies in a prospective RBD longitudinal cohort in China.

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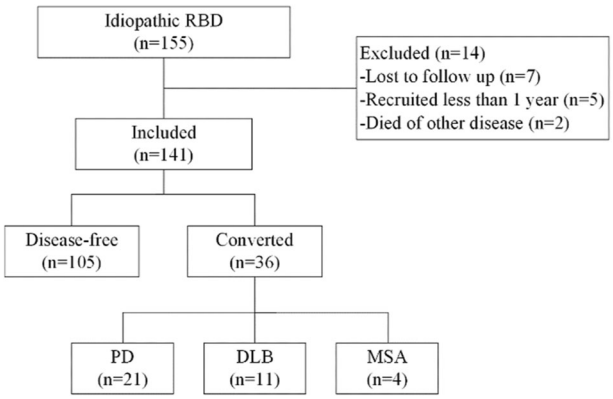

Fig. 1 | Flow chart of the study. Of the 155 enrolled iRBD, 14 were excluded and 141 were included in the final analysis. Thirty-six patients converted to α-synucleinopathies, including 21 PD, 11DLB, and 4 MSA. PD Parkinson's disease, DLB dementia of Lewy bodies, MSA multiple system atrophy.

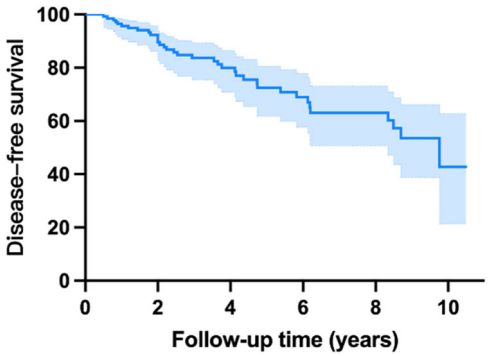

Fig. 2 | Probability of survival from idiopathic/isolated rapid eye movement sleep behavior disorder to overt α-synucleinopathies (i.e., Parkinson's disease, multiple system atrophy, and dementia with Lewy bodies). The cumulative incidences were 16.30% after 3 years, 27.57% after 5 years, 57.20% after 10 years.

Results

Participants and disease outcomes at follow-up

Among 155 patients with iRBD in our cohort. 141 (90.97%) participants fulfilled the inclusion criteria and were included in the current study. 14 subjects were excluded from the analysis, including 7 patients lost in follow-up, 2 patients died of other diseases before the first follow-up, and 5 patients recruited less than one year. 11 of 141 participants died after the last follow-up and were included in the analysis. The mean follow-up time (from baseline to the last interview) was 4.14 ± 2.88 years.

During follow-up, 36 (25.53%) patients developed α-synucleinopathies (PD, DLB, MSA), and 105 (74.47%) patients remained disease-free till the last visit or before death (Fig. 1). The mean interval from the baseline interview to the disease phenoconversion is 3.59 ± 2.53 years. The cumulative incidences were 16.30% after 3 years, 27.57% after 5 years, 57.20% after 10 years (Fig. 2). The diagnosis included PD in 21 patients (58.33%), DLB or dementia in 11 patients (30.56%), and MSA in 4 patients (11.11%).

Demographics, environmental and lifestyle factors

As shown in Table 1, at the baseline, the mean age of iRBD patients was 66.66 ± 7.13 years old and 104 (73.76%) of the patients were male. The average duration of iRBD symptoms was slightly longer ($p = 0.048$) in the converters (9.17 ± 7.92 years with a median duration of 7 years) than in non-converters (6.16 ± 7.01 years with a median duration of 3.25 years). Age, sex ratio, educational levels, and follow-up years were not significantly different between iRBD converters and non-converters.

In general, no association was observed between environmental exposures and disease phenoconversion. For lifestyle habits, iRBD patients who had drunk tea ever had a two-fold lower risk of converting to α-synucleinopathies (adjusted HR = 0.35, 95% confidence interval [CI] = 0.17–0.73, $p = 0.005$) (Fig. 3). Those who keep the habit of drinking tea and drinking daily exhibited a similar lowered risk for phenoconversion (adjusted HR = 0.34, 95% CI = 0.16–0.74, $p = 0.007$, and adjusted HR = 0.32, 95% CI = 0.14–0.72, $p = 0.006$ respectively). Although the analysis model for factors of RBD conversion was adjusted for the duration of RBD symptoms, the Unified Parkinson's Disease Rating Scale Part III (UPDRS-III) and Montreal Cognitive Assessment (MoCA) were adjusted for the results to further reduce the influence of mild motor symptoms and cognitive impairment on the period of conversion between conversion and non-conversion groups. The results of risk factors were similar to those of the primary analyses (Supplementary Table S1). However, no association between the total amount of tea consumed and conversion risk was observed though non-converters drank more cups/w-years of tea than converters. Still, the difference was not statistically significant (327.82 ± 535.24 vs 272.10 ± 605.27, $p = 0.337$).

None of the ever-smoking, current-smoking, and pack-years was associated with disease phenoconversion. Drinking alcohol ever and currently was not associated with disease conversion. Converters had slightly more but not statistically significantly drinking servings/week-years than non-converters (185.50 ± 370.39 vs 176.03 ± 392.50, $p = 0.151$). In addition, there was no statistically significant association between coffee use or exercise and phenoconversion.

Family History of Parkinsonism and dementia

A greater risk of developing α-synucleinopathies was found in patients with a positive family history of parkinsonism (adjusted HR = 2.79, 95% confidence interval [CI] = 1.11–7.06, $p = 0.030$) (Fig. 4). There was no discernible variation in the positive family history of dementia between converters and non-converters.

Comorbidity and Medication History

In terms of comorbidities, no statistically significant differences were found in self-reported hypertension, cardiovascular disease, diabetes, hyperthyroidism, stroke, encephalitis, epilepsy, and depression/anxiety between converters and non-converters (Supplementary Table S2). Neither was observed in the use of antihypertensive agents, β-blockers, calcium channel receptor antagonists, antidiabetic drugs, uric acid-lowering drugs, lipid-lowering drugs, antiplatelet drugs, antidepressants, melatonin and melatonin receptor agonists, and clonazepam.

Discussion

The current study demonstrated that most known risk factors for PD and iRBD were not associated with an increased risk for phenoconversion from iRBD to a-synucleinopathies. However, iRBD patients with ever tea drinking had a two-fold decrease in risk of being converted, while a positive family history of parkinsonism had a two-fold increase in risk for conversion. Our finding suggests that tea drinking may specifically modify the disease progression and reduce the risk for or delay phenoconversion, at least in Chinese.

Previous studies have shown that factors associated with increased risk for PD, e.g. aging[11,12], gender[15], CO poisoning[8], and pesticide exposure[6–8], are also risk factors for iRBD and its progressing to clinical manifestation. Interestingly, when our prospective study specifically comparing the iRBD patients with and without phenoconversion to α-synucleinopathies during follow-up, most factors associated with increased risk for both PD and iRBD were not significantly associated with a faster rate of conversion except duration of iRBD. These findings suggest that these risk factors may be only associated with overt dopaminergic degeneration but not accelerated conversion from iRBD to α-synucleinopathies. However, this notion needs to be validated in future studies with a large sample size.

Consistent with the previous multicenter study in iRBD[11], we found a close relationship between a positive family history of parkinsonism and clinical phenoconversion. In fact, studies have shown that patients with

Table 1 | Demographics, environmental and lifestyle factors

	Converters (*n* = 36)	Non-converters (*n* = 105)	Age-/Sex-/RBD duration Adjusted HR (95% CI)	*P* value
Age	66.37 ± 7.91	66.77 ± 6.88	0.99 (0.94–1.04)	0.619
Male	25 (75.8%)	74 (72.5%)	0.92 (0.43–1.97)	0.828
Educational years	12.33 ± 3.53	12.07 ± 3.95	1.06 (0.96–1.17)	0.232
Duration of RBD symptoms	9.17 ± 7.92	6.16 ± 7.01	1.04 (1.001–1.09)	**0.046**
Family history of PDS or dementia	9 (25.0%)	17 (16.2%)	2.04 (0.88–4.73)	0.098
Family history of PDS	6 (16.7%)	8 (7.6%)	2.79 (1.11–7.06)	**0.030**
Family history of dementia	3 (8.3%)	11 (10.5%)	0.87 (0.25–3.10)	0.831
CO poisoning	12 (33.3%)	15 (14.3%)	1.64 (0.81–3.35)	0.173
Head injury	2 (5.6%)	12 (11.4%)	0.87 (0.20–3.71)	0.849
Occupational herbicide/insecticide	1 (2.8%)	3 (2.9%)	7.48 (0.83–67.14)	0.072
Non-occupational herbicide/insecticide	6 (16.7%)	10 (9.5%)	1.57 (0.65–3.84)	0.319
Chemical solvent	0 (0)	5 (4.8%)	–	0.974
Heavy metal	1 (2.8%)	2 (1.9%)	1.97 (0.25–15.34)	0.518
Chemical aerosol	0 (0)	3 (2.9%)	–	0.975
Trichloroethylene	0 (0)	2 (1.9%)	–	0.981
Rotenone	0 (0)	0 (0)	–	–
Paraquat	0 (0)	1 (1.0%)	–	0.983
Smoking, ever	14 (38.9%)	47 (44.8%)	0.56 (0.26–1.22)	0.146
Smoking, current	8 (22.2%)	26 (25.0%)	0.49 (0.20–1.25)	0.137
Smoking, pack-years	12.28 ± 21.58	13.13 ± 22.02	0.997 (0.98–1.02)	0.748
Alcohol drinking, ever	10 (27.8%)	35 (33.3%)	0.76 (0.34–1.67)	0.487
Alcohol drinking, current	7 (19.4%)	16 (15.4%)	1.14 (0.45–2.90)	0.780
Alcohol drinking, cup/w-years	185.50 ± 370.39	176.03 ± 392.50	1.001 (1.00–1.002)	0.151
Tea drinking, ever	15 (41.7%)	61 (58.1%)	0.35 (0.17–0.73)	**0.005**
Tea drinking, current	11 (30.6%)	48 (46.2%)	0.34 (0.16–0.74)	**0.007**
Tea drinking, daily	9 (25.0%)	44 (42.3%)	0.32 (0.14–0.72)	**0.006**
Tea drinking, cup/w-years	272.10 ± 605.27	327.82 ± 535.24	1.00 (0.999–1.00)	0.337
Coffee, ever	6 (16.7%)	15 (14.3%)	0.997 (0.41–2.41)	0.994
Coffee, cup/w-years	18.50 ± 62.18	7.88 ± 38.56	1.003 (0.998–1.009)	0.241
Exercise, ever	27 (75.0%)	90 (85.7%)	0.96 (0.43–2.12)	0.919
Exercise, daily	21 (58.3%)	52 (49.5%)	1.48 (0.72–3.08)	0.289

Bold values denote statistical significance at the $P < 0.05$ level. *RBD* rapid eye movement sleep behavior disorder, *HR* hazard ratio, *CI* confidence interval.

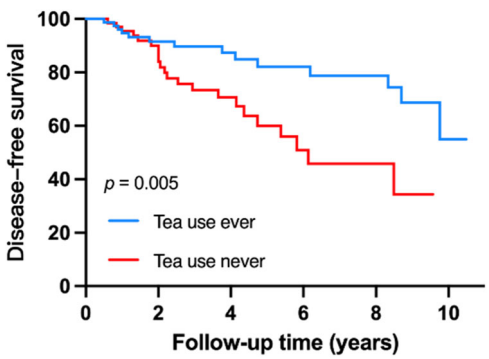

Fig. 3 | Comparison in the survival proportion between patients with and without tea use history. IRBD patients with tea use history had lower risk of developing α-synucleinopathies (adjusted HR = 0.35, 95% confidence interval [CI] = 0.17–0.73, $p = 0.005$).

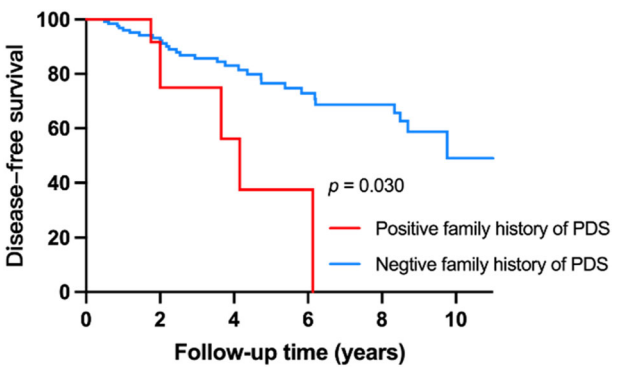

Fig. 4 | Comparison in the survival proportion between patients with and without positive family history of PDS. IRBD patients with positive family history of parkinsonism had increased risk of developing α-synucleinopathies (adjusted HR = 2.79, 95% confidence interval [CI] = 1.11–7.06, $p = 0.030$).

RBD partially share some of the genetic background of PD and DLB, including *SCARB2* (rs6812193), *MAPT* (rs12185268)[5], *GBA*[16], and *SNCA* variants[17]. Moreover, iRBD with *GBA*[18] or *SNCA*[17] variants were reported to potentially correlate with the rate of conversion to synucleinopathies. Therefore, genetic risk factors may play a role not only in the development of iRBD but also in its phenoconversion. Our previous study has shown that PD patients with *LRRK2* and *GBA* risk variants had a higher likelihood ratio and fast conversion[19]. Further studies are needed to clarify the role of genes in disease fast conversion.

The key finding of this study is that iRBD patients with a history of tea consumption were less likely to be converted, suggesting that present or daily tea drinking may slow the disease progression. Tea consumption was first found to reduce the risk of PD in a study with the Chinese population in 1998[20]. Following that, many studies from different regions have investigated if tea exerts a protective effect on PD with different conclusions[13,21–24]. Although most studies in the Caucasian population found a negative results, there was one study found that tea drinking had a protective influence on LRRK2 mutation carriers in non-Asians[25]. Therefore, these studies support the notion that tea drinking has protective effects in individuals with increased risk for PD, particularly in populations with regular habits of tea drinking in Asian.

The exact mechanism of the possible protective role of tea on iRBD progression is still unclear. Some scholars believe that it was caffeine that has an antagonistic effect on adenosine A_{2A} receptors that act as a part[22,23]. Others thought that it was tea polyphenols rather than caffeine that were responsible for the protective effect against dopaminergic neurotoxicity and modification of oxidative stress[21,24]. A prior study has demonstrated that tea polyphenols protect against dopamine (DA)-related toxicity through direct abrogation of DA-induced toxicities as well as regulation of anti-oxidative signaling pathways in vitro and in vivo PD models[26]. Moreover, a study suggested that fermented tea had therapeutic value in an MPTP-induced PD mouse model for its anti-neuroinflammatory, anti-apoptosis, antioxidant, and neuroprotective properties[27]. In contrast, no difference in baseline caffeinated tea consumption between converters and non-converters in patients with iRBD was also reported[12]. The disparity could be attributed to a variation in diet culture differences between the West and the East. It is known that coffee intake is more common in Caucasians but Chinese prefer drinking tea[28], which is consistent with a low percentage of patients with iRBD who drank coffee in this study. Moreover, no association between coffee intake and RBD phenoconversion was found in the previous study[12]. Therefore, we consider that the caffeine component of tea may not be the main reason for its effect on disease conversion. Accordingly, the protective effect of tea consumption in iRBD may provide prospects for α-synucleinopathies prevention and serve as the foundation for future interventional trials.

It was suggested that lower PD risk and smoking had a dose-response relationship[29]. Meta-analysis also showed substantial evidence that smokers are less likely to develop PD[30]. However, a previous study has found that smoking, on the other hand, is a potential risk factor for iRBD[6]. In addition, no link was reported between smoking and phenoconversion risk in a large multicenter RBD study[12], which is similar to our finding. Therefore, smoking is less likely associated with phenoconversion.

In terms of comorbidities and medications, contrary to our results, previous studies found that β2-adrenoreceptor agonists[12], nitrate derivatives[12], lipid-lowering drugs[12], and antidepressants[31] were associated with phenoconversion of iRBD. This might be due to variations in the time and dosage of medication used in the studies.

Several limitations in this study should be noted. First, it was a single-center study of the Chinese population and could not represent the general population. Second, patients' reports on environment and lifestyle exposures were based on their subjective recollection, which could lead to recall bias. Third, the questionnaire for assessing physical activity in this manuscript was custom-made instead of established. Fourth, we paid more attention to the amount and frequency of tea consumed but did not inquire about specific classifications of tea (green, black, or others). It is likely most people drink different types of tea rather than fixed types. Finally, some environmental exposures and lifestyle factors were reported only in fewer patients, such as pesticide exposure, weakening the power of the statistics. Therefore, future multicenter prospective investigation is warranted.

In conclusion, our prospective study found that iRBD with a positive family history of PDS had a higher risk for conversion to α-synucleinopathies, while tea drinking was associated with a decreased risk for phenoconversion. Although the mechanistic aspects may not be elucidated in this study focusing on the assessment of risk associations, its results shed light on its potential application in disease-modifying effects of tea drinking for phenoconversion of iRBD.

Methods

Subjects

Subjects aged 50 years or older with iRBD were consecutively recruited from the Department of Neurology at Xuanwu Hospital Capital Medical University from October 2012 to October 2022. All patients were diagnosed based on video-polysomnography (v-PSG) and met the International Classification of Sleep Disorders-3 criteria[32] for RBD. Individuals diagnosed with secondary RBD, such as those associated with narcolepsy, brainstem lesions, or medication use (mostly antidepressants) were excluded. A thorough neurological evaluation was performed on each participant to rule out the presence of any symptoms or signs of dementia or parkinsonism. By October 2022, 155 patients with iRBD were included in this study.

Baseline questionnaires

A standardized structured questionnaire was designed to assess the presence of environmental exposure and lifestyle habits at baseline interview. Demographic information was collected, including gender, age, and education levels. Duration of RBD symptoms and family history of parkinsonism or dementia were reported by patients or their family members. RBD Questionnaire-Hong Kong (RBDQ-HK), the UPDRS-III, and MoCA scores were obtained through face-to-face interviews by physicians. Histories of CO poisoning, head injury, and exposures to noxious agents, chemical solvents, heavy metals, chemical aerosol, trichloroethylene, rotenone, and paraquat were collected. Lifestyle variables were also collected for smoking history, alcohol consumption, tea and coffee intake, and exercise status. The quantity of cigarettes daily use, years of smoking, the number of cups of alcohol, tea, and coffee consumed weekly and duration were recorded. The number of packs smoked every day (20 cigarettes per pack) multiplied by the number of years smoked was used to calculate pack-year. Cups/week–year was calculated by multiplying the average number of cups per week by the number of years for consuming tea or coffee. Servings/week-year was calculated by multiplying the average number of servings per week by the number of years of drinking alcohol. For reference, a serving is a can or bottle of beer, a glass of wine, or a shot of liquor. Smoking or drinking beverages were categorized as "ever" (past and current) and "never". Participants who had smoked fewer than 100 cigarettes (five packs) or drank alcohol less than 100 times by the time of the questionnaire were considered as "never". Those who did not drink tea or coffee at least once a week for six months were defined as never drinking. The status of smoking and drinking (alcohol, tea, coffee) were divided into "past", "current" and "never". The frequency of tea drinking and physical exercise, as well as exercise types (cycling, running, boxing, dancing, hiking, walking, and others), were also collected. Information about previous medical histories of hypertension, diabetes, cardiovascular disease (CVD), hyperthyroidism, stroke, encephalitis, epilepsy, depression, and anxiety were obtained. Besides, history of medication using antihypertensive agents, β-blockers, calcium channel receptor antagonists, antidiabetic drugs, antipsychotic drugs, antiplatelet drugs, antiepileptic drugs, antidepressants, melatonin, and melatonin receptor agonists, clonazepam were also collected in the baseline assessment.

Follow-up and phenoconversion

We prospectively followed up subjects with iRBD by in-person interview or telephone interview. The phenoconversion to define parkinsonism or dementia was diagnosed by at least two experienced movement disorder specialists. In our cohort, only iRBD patients underwent at least one follow-

up more than one year after the baseline assessment were included in the current analysis. The date of the last visit and the onset time before the final diagnosis of neurodegenerative diseases were recorded. For patients with parkinsonism-first manifestations, clinical diagnoses of PD or MSA were made according to the diagnostic criteria described by the Movement Disorder Society (MDS) and Gilman et al., respectively[33,34]. For patients with dementia-first manifestations, the diagnosis of DLB was based on the consensus criteria[35,36], depending on the conversion year. If both parkinsonism and dementia were diagnosed at the same visit, the diagnosis of Parkinson's disease dementia (PDD) or DLB would be established according to the one-year principle. It should be noted that mild cognitive impairment (MCI) was not considered a phenoconversion in this study.

Standard protocol approvals, registrations, and patient consent

Informed consent was obtained from all participants. The protocols of this study have been approved by the Research Ethics Committee of Xuanwu Hospital of Capital Medical University (Ethics approval No. [2012]006, No. [2022]047).

Statistical analysis

SPSS version 25.0 (IBM, Corp.) was used for statistical analysis. For descriptive statistics, continuous variables were summarized as mean ± standard deviation (SD), whilst categorical variables were presented as frequencies (percentages). We conducted comparisons between groups of baseline characteristics using an unpaired two-tailed Student t-test or the Wilcoxon rank sum test for continuous variables. For categorical variables, the $\chi 2$ test was used. We performed Cox proportional hazard analysis to evaluate the variables of environmental and lifestyle factors between those who phenoconverted to α-synucleinopathies and those who remained iRBD, adjusted for age, sex, and iRBD duration.

Data availability

The data underlying this article cannot be shared publicly due to the privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author.

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Author contributions

P.C, W.M, and Y.-N.C: supervision of the project. Y.Y: conceptualization, data analysis, and writing the original draft. Y.L and W.M: conceptualization and methodology. Y.H and S.-Q.Z: interpretation of data. Y.L, Y.Y, Y.-J.Z, and X.-N.L: acquisition of data. P.C, Y.L, and H.Z: writing review and editing. All authors have read and approved the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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